REMARKS

Claims 1, 3-8, 20 and 22-25 are pending in the present application. By virtue of this response, claims 1 and 20 have been amended, and new claims 51 and 52 have been added. Accordingly, claims 1, 3-8, 20, 22-25, and 51-52 are currently under consideration. Support for the amendment of claim 1 is found in the specification, such as in paragraph [0012], Example 7, and original claim 20. Support for the amendment of claim 20 is found in the specification, such as in paragraph [0012] and original claim 1. Support for new claims 51 and 52 is found in the specification, such as in paragraph [0012]. No new matter is added.

With respect to all claim amendments, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in a future continuation and/or divisional application.

Telephone Interview

Applicants thank Examiner Yunsoo Kim for extending the courtesy for a telephone interview on August 25, 2008, with Applicants' representative Jie Zhou and Craig G. Svoboda, and for providing helpful suggestions, which are reflected in this response. Rejections under 35 U.S.C. §103(a) and nonstatutory obviousness-type double patenting were discussed during the telephone interview.

Claim Rejection – 35 U.S.C. § 103(a)

Claims 1, 3-8, 20 and 22-25 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over WO 97/26909 ("the '909 publication"), in view of U.S. Pat. No. 5,994,511 ("the '511 patent"). The Examiner states that it would have been obvious to one of the ordinary skill in the art at the time the invention was made to stabilize rhuMAbE25 as taught by the '511 patent with a formulation comprising a buffer comprising histidine, arginine and polysorbate as taught by the '909 publication since one skilled in the art would have been motivated to do so and would have a

reasonable expectation of success in producing the claimed invention from the teachings of the references.

Applicants respectfully traverse the rejection.

As amended, claim 1 (from which claims 3-8 and 22-25 depend) is directed to a stable liquid formulation comprising 120 to 260 mg/ml rhuMAbE25, 100 to 200 mM arginine-HCI, 10 to 100 mM histidine, 0.01 to 0.1% polysorbate, where the formulation has a pH ranging from 5.5 to 6.0, has a kinematic viscosity of about 50 cs or less, an osmolarity ranging from 200 mOsm/kg to 450 mOsm/kg and a turbidity of 0.30 O.D. or less mean absorbance as measured by a 1-cm quartz cuvette using an Hewlett-Packard 8453 diode array spectrophotometer at 340-360 nm. As amended, claim 20 (from which claims 22-25 depend) is directed to a stable liquid formulation comprising about 150 mg/ml rhuMAbE25, 200 mM arginine-HCI, 20 mM histidine, 0.01% to 0.1% polysorbate, where the formulation has a pH of 6.0 and a turbidity of 0.30 O.D. or less mean absorbance as measured by a 1-cm quartz cuvette using an Hewlett-Packard 8453 diode array spectrophotometer at 340-360 nm.

The '909 publication teaches liquid formulations for factor IX, and the formulations comprise factor IX, tonicity modifiers, cryoprotectants, and optionally, a buffering agent and/or other excipients which further stabilize factor IX. See page 5, lines 22-24. This reference further provides that arginine or histidine among other salts, sugars, polyols, and amino acids may be used as a tonicity modifier. See page 5, lines 27-30. The reference focuses on the formulations for factor IX, and does not teach or suggests that the formulations for factor IX may be used for other proteins, such as anti-IgE antibody rhuMAbE25. The reference emphasizes that each protein has its unique property and formulations developed for one protein may not be used for another protein. See page 2, line 23 to page 3, lines 20. For example,

> While the possible occurrence of protein instabilities is widely appreciated, it is *impossible to predict particular instability problems of a particular protein*. Any of these instabilities can result in the formation of a protein, protein by-product, or derivative

having lowered activity, increased toxicity, and/or increased immunogenicity. Indeed, protein precipitation may lead to thrombosis, non-homogeneity of dosage form and amount, as well as clogged syringes. Also, specific to factor IX, there are several post-translational modifications (for example. the ganuna carboxylation of certain glutamic acid residues in the N-terminus and the addition of carbohydrate) all of which provide potential sites that may be susceptible to modification upon storage. Thus, the safety and efficacy of any pharmaceutical formulation of a protein is directly related to its stability. Maintaining that stability in a liquid dosage form is generally different from a lyophilized dosage form because of greatly increased potential for molecular motion and therefore increased probability of molecular interactions. Maintaining stability in a highly concentrated form is also different because of the propensity for aggregate formation at high protein concentrations.

When developing a liquid formulation, many factors are taken into consideration. Short-term. *i.e.*, less than six months, liquid stability generally depends on avoiding gross structural changes, such as denaturation and aggregation. These processes are described in the literature for a number of proteins, and many examples of stabilizing agents exist …. *It is well known that an agent effective at stabilizing one protein actually acts to destabilize another.* Once the protein has been stabilized against gross structural changes, developing a liquid formulation for long-term stability (greater than six months, for example) depends on further stabilizing the protein from types of degradation specific to that protein. More specific types of degradation may include, for example, disulfide bond scrambling, oxidation of oligosaccharides and/or certain residues, deamidation, cyclization, and the like. Although it is not always possible to pinpoint the individual degradation species, assays are developed to monitor subtle changes so as to monitor the ability of specific excipients to uniquely stabilize the protein of interest.

(page 2, line 9 to page 3, line 8) (emphasis added).

Accordingly, the '909 publication does not teach or suggest a stable liquid formulation for rhuMAbE25 comprising arginine-HCl, histidine and polysorbate and having a pH ranging from 5.5 to 6.0 as claimed. The '511 patent does not cure this deficiency of the '909 publication. While the '511 patent teaches anti-IgE antibodies, it does not teach liquid formulations of such antibodies at a concentration of 120-260 mg/ml. The '511 patent teaches general excipients or stabilizers including buffer agents, stabilizing agents, preservatives, isotonifiers, non-ionic detergents, antioxidants and other miscellaneous additives. *See* col. 52, lines 54-65. The '511 patent does not teach or suggest that a formulation comprising the specific combination of arginine-HCl, histidine and polysorbate with a pH ranging from 5.5 to 6.0 as claimed provides a stable liquid formulation for highly concentrated rhuMAbE25 with low turbidity.

In view of the disclosures in these references, one skilled in the art would not have been motivated to combine the teachings of the '909 publication and the '511 patent to arrive at the claimed invention, *i.e.*, the stable liquid formulations for rhuMAbE25 as claimed. In particular, a skilled artisan would not have been motivated to use a liquid formulation specifically developed for factor IX as a stable liquid formulation for rhuMAbE25. The '909 publication emphasizes the importance that a liquid formulation has to be developed for each specific therapeutic protein in view of different structures, functions, and therapeutic use. As noted above, the reference indicates that an agent effective at stabilizing one protein could act to destabilize another protein. These disclosures teach away from using the liquid formulation developed for factor IX, a protein involved in blood clotting process, to formulate a stable liquid formulation for an anti-IgE antibody rhuMAbE25. Thus, a skilled artisan would not have been motivated to use the formulation disclosed in the '909 publication to rhuMAbE25.

Additionally, neither the '909 publication nor the '511 patent provides a reasonable expectation of success for producing the stable liquid formulations for rhuMAbE25 with low turbidity as claimed. In particular, neither reference appreciated the high turbidity problem associated with liquid formulations containing high concentrations of rhuMAbE25. Further, the '909 publication does not teach or suggest that arginine-HCl, among all other salts, sugars, polyols, and amino acids, can be used for reducing turbidity of a liquid formulation comprising high

concentration of rhuMAbE25. Without this teaching, one skilled artisan would not know which excipients among all the excipients taught in the '909 publication or known in the art could be successfully used for reducing turbidity of a liquid formulation containing high concentration of rhuMAbE25.

As indicated in the declaration by Jun Liu ("the Liu Declaration") and Examples 5 and 6 in the present application, the liquid formulations containing arginine-HCl have the least turbidity among all the salts tested and are more stable than the formulation containing $MgCl_2$ and $CaCl_2$. To develop a stable liquid formulation for rhuMAbE25, the inventors need to identify excipients that reduce the high turbidity and maintain stability of the liquid formulations for high concentrations of rhuMAbE25. In view that antibodies specific for different antigens even have different properties as demonstrated in the Liu Declaration, one skilled in the art would not reasonably expect that the formulations for factor IX disclosed in the '909 publication could provide a stable liquid formulation with low turbidity for rhuMAbE25 at 120 mg/ml to 260 mg/ml.

Applicants respectfully disagree with the Examiner that having low turbidity, kinematic viscosity about 50cs, and osmotic pressure from 270-328 mOsm are inherent property of the protein formulation comprising 10 mM histidine, 16 mM arginine-HCl at pH 7.0 and 0.05% polysorbate. As indicated in the '909 publication and demonstrated in the Liu Declaration, different proteins behave differently in liquid formulations. For example, arginine-HCl, which reduced turbidity for a rhuMAbE25 liquid formulation, increased the turbidity for the anti-HER2 antibody in the same formulation as shown in the Liu Declaration. Accordingly, having the turbidity, viscosity, and osmolarity ranges specified in the claims are not inherent property of a liquid formulation comprising 100-200 mM arginine-HCl, 10 mM to 100 mM histidine, 0.01 to 0.1% polysorbate, pH 5.5 to 6.0 for <u>any proteins</u>.

In view of the above, Applicants respectfully submit that the Examiner has not established a *prima facie* case of obviousness, and claims 1, 3-8, 20 and 22-25 are not obvious over the '909 publication in view of the '511 patent. Applicants respectfully request that the rejection be withdrawn.

Double Patenting

Claims 1, 3-8, 20 and 22-25 stand rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1-4, 7-13, 22-27,31-34, 37-42, 48, 51-56, 58 and 59 of U.S. Patent No. 6,875,432 ("the '432 patent") in view of US 2004/109243A1 ("the '243 publication").

Applicants respectfully traverse.

As amended, claim 1 (from which claims 3-8 and 22-25 depend) is directed to a stable liquid formulation comprising 120 to 260 mg/ml antibody rhuMAbE25, 100 to 200 mM arginine-HCl, 10 to 100 mM histidine, 0.01 to 0.1% polysorbate, and the formulation has a pH ranging from 5.5 to 6.0, a kinematic viscosity of about 50 cs or less, an osmolarity ranging from 200 mOsm/kg to 450 mOsm/kg and a turbidity of 0.30 O.D. or less mean absorbance as measured by a 1-cm quartz cuvette using an Hewlett-Packard 8453 diode array spectrophotometer at 340-360 nm. As amended claim 20 (from which claims 22-25 depend) is directed to a stable liquid formulation comprising about 150 mg/ml rhuMAbE25, 200 mM arginine-HCl, 20 mM histidine, 0.01% to 0.1% polysorbate, and the formulation has a pH of 6.0 and a turbidity of 0.30 O.D. or less mean absorbance as measured by a 1-cm quartz cuvette using an Hewlett-Packard 8453 diode array spectrophotometer at 340-360 nm.

Applicants respectfully submit that claims 1, 3-8, 20 and 22-25 in the present application are not obvious over claims 1-4, 7-13, 22-27, 31-34, 37-42, 48, 51-56, 58 and 59 of the '432 patent in view of the '243 publication. Claims in the '432 patent do not teach or suggest that a specific combination of excipients for formulations comprising 100 to 200 mM arginine-HCl, 10 to 100 mM histidine, and 0.01 to 0.1% polysorbate, and a pH ranging from 5.5 to 6.0. One skilled in the art would not be motivated to select this specific combination of excipients among all the known salts, buffers, and surfactants as claimed in the '432 patent. The '243 publication does not cure this deficiency of the '432 patent. Although the '243 publication teaches using a combination of arginine and histidine for liquid formulations, this reference only teaches use of a concentration for both arginine and histidine at 15 mM to 60 mM, and states that variations for histidine

concentrations ranging from 15 mM to 60 mM and arginine concentrations from 15 mM to 60 mM did not affect the overall quality of the product (i.e., antibody ABX-IL8). See Example 15, paragraph [0100]. As shown in the '432 patent, having higher salt concentration (such as arginine-HCl) in the formulation is important for reducing viscosity of the liquid formulation for rhuMAbE25. See Example 3 and Figure 3. This clearly demonstrates that rhuMAbE25 has properties different from antibody ABX-IL8; and one skilled in the art would not have been motivated to combine excipients disclosed in the '243 publication into the formulation claimed in the '432 patent for rhuMAbE25.

In addition, as shown in the Liu Declaration, the turbidity problem for liquid formulations containing high concentration of rhuMAbE25 is unique to antibody rhuMAbE25. A skilled artisan would not be able to predict which excipient would be effective for reducing turbidity. Neither the '432 patent nor the '243 publication appreciated the problem of turbidity for highly concentrated rhuMAbE25 formulations. Accordingly, based on the claims in the '432 patent and disclosures in the '243 publication, one skilled in the art would not have a reasonable expectation of success in producing the formulations for high concentrations of rhuMAbE25 having reduced turbidity as claimed in the present application.

Further, claims in the '432 patent do not teach or suggest to use a pH ranging from 5.5 to 6.0 or pH 6.0 for liquid formulations comprising high concentration of rhuMAbE25. In contrast, claim 31 of the '432 patent shows that the preferred pH range is either a pH of about 4.2 to 5.3 or 6.5 to about 12.0. As demonstrated in the Liu Declaration, a formulation having a pH ranging from 5.5 to 6.0 provides advantage for maintaining stability of rhuMAbE25 in liquid formulations. This advantage for rhuMAbE25 liquid formulations was not appreciated by the '432 patent or the 243 publication.

In view of the above, claims 1, 3-8, 20 and 22-25 are not obvious over claims 1-4, 7-13, 22-27, 31-34, 37-42, 51-56, 58 and 59 of the '432 patent in view of the '243 publication. Accordingly, Applicants respectfully request that the nonstatutory obviousness-type double patenting rejection be withdrawn.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 146392005600. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

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